REMARKS

Claims 65-144 are now pending in the case, all previously pending claims having been cancelled and new claims 65-144 added by the above amendment. The new claims are generally supported throughout the specification and by the cancelled claims. For example, the limitations regarding percent purity of budesonide are supported at page 7, lines 21-23, of the specification. The limitations regarding the size of the particles are supported, e.g., at page 5, lines 6-9, at page 7, lines 1-3, and at page 10, lines 5-9. The limitations regarding sterilization conditions are supported at page 3, line 29, to page 4, line 5, and at page 5, line 15, to page 6, line 21. The limitations regarding the suspension are supported at page 8, lines 8-11. The limitations regarding the surfactant are supported at page 8, line 13, to page 9, line 2. The limitations regarding the pH regulating agent are supported at page 9, lines 4-10. The limitations regarding the chelating agent are supported at page 9, lines 11-14. The limitations regarding agents that are added to make the suspension isotonic are supported at page 9, lines 16-17. The limitations regarding the thickening agent are supported at page 9, line 19, to page 10, line 3. The limitations regarding treatment of specified disease conditions are supported, e.g., at page 10, line 24, to page 11, line 3. No new matter has been added.

Claim objections

The informalities in claims 57-60 pointed out by the Office action at page 2 have been rendered moot by the above cancellation of these claims.

Rejections under 35 USC §112, first paragraph

The rejection of claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54, and 56-64 under the first paragraph of 35 USC §112 is rendered moot by the cancellation of these claims. None of the newly added claims contains the "unknown foreign steroids" limitation that was the basis for this rejection. Withdrawal of the rejection is therefore requested.

Rejection under 35 USC §112, second paragraph

The rejection of claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54, and 56-64 under the second paragraph of 35 USC §112 is rendered moot by the cancellation of these claims. None of the newly added claims contains the "unknown foreign steroids," "known foreign steroids," and "essentially the same chemical purity and physical form as the particles before sterilization" limitations that were the bases for this rejection. Withdrawal of the rejection is therefore requested.

Rejections under 35 USC §103(a)

All of the previously pending claims were rejected as obvious in view of Jakupovic et al. (WO 96/32095) and Bussey et al. (J. Parenter. Sci. Tech., 1983), and/or that combination in view of either Sequieira (US Patent No. 5,837,699) or Radhakrishnan et al. (US Patent No. 5,192,528). As all of these claims have been cancelled, the rejections are moot. All of the presently pending claims are limited to a sterile powder composition at least 98.5% of which is pure budesonide (or an ester, acetal or salt thereof), or an aqueous suspension of such a powder, or a method of treatment utilizing such a powder or suspension. To the extent that the same prior art may be applied to reject the presently pending claims, Applicants traverse.

The Office action at pages 5-6 cites Jakupovic as teaching budesonide particles of a particular size range and cites Bussey as teaching the sterilization of (gluco)corticosteroid powders by ^{60}Co irradiation or by ethylene oxide. According to the Office action, it would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize the respirable, dry powders disclosed by Jakupovic by either irradiation or treatment with ethylene oxide.

First, Applicants note that the claims all require that the budesonide powder be "pharmaceutically acceptable." This term excludes compositions containing contaminants that render the compositions unacceptable for pharmaceutical use. Sterilization with ethylene oxide, a toxic compound, is presently considered unsuitable for pharmaceutical use because it results in residual traces of ethylene oxide in the sterilized preparation. See the specification at page 1,

lines 11-21. In fact, the problems with ethylene oxide were what motivated Bussey to experiment back in 1985 with irradiation as an alternative means to sterilize corticosteroid powder. See Bussey's discussion at page 51, column 1, of the "mutagenic and possible carcinogenic properties and problem with residues" when ethylene oxide is used. Rather than teach one of ordinary skill that ethylene oxide is a suitable means to sterilize corticosteroids for pharmaceutical use, Bussey plainly teaches away from using this sterilization method. Furthermore, even if Bussey could somehow be read as suggesting use of ethylene oxide, it is clear that a budesonide powder that had been treated with ethylene oxide cannot be considered "pharmaceutically acceptable," and so does not fall within the present claims.

Second, Applicants note that the present claims all require a level of purity of at least 98.5% budesonide, and some require even higher levels of purity. The irradiation technique taught by Bussey would not generate a budesonide composition that meets this purity limitation. Bussey teaches that one should use a minimum ^{60}Co (i.e., γ) irradiation dose of 1.33 Mrads to sterilize various corticosteroids. See the abstract of Bussey on page 51, as well as the disclosure at page 53, right column. Bussey worked with corticosteroids other than budesonide, so does not disclose what level of degradation would be produced upon γ-irradiation of budesonide in particular. For that information, one must look to Applicants' specification.

As disclosed in Comparative Example 8 in the present specification, Applicants tested two levels of γ-irradiation of budesonide to determine the chemical stability of budesonide under such conditions. The two doses tested were 7.8 and 31.9 kGy, corresponding to 0.78 and 3.19 Mrad. See Table 8. Although Bussey's 1.33 Mrad dose was not tested in this experiment, one can see that even a dose as low as 7.8 kGy (0.78 Mrad) reduced the budesonide content of the composition to 97.9%. Bussey's 1.33 Mrad dose would presumably have produced even more degradation of the budesonide, lowering the purity to some point between 97.9% (observed with 0.78 Mrad) and 95% (observed with 3.19 Mrad). Thus, even if it would have been obvious, as the Office action contends, to use Bussey's irradiation technique for sterilization of budesonide, the resulting composition would not meet the present claim limitation requiring at least 98.5% purity. Nothing in any of the cited art teaches otherwise. Nor does any of the cited

art teach any other method of sterilization, whether by irradiation or otherwise, that would be expected to produce a budesonide composition that falls within any of the present composition claims. Thus, it could not have been obvious to one of ordinary skill how to generate the claimed sterile compositions with the required degree of purity. Withdrawal of the rejection is respectfully requested.

Applicants note for the record that a statement made in the Response filed by Applicants on January 21, 2004, concerning FDA requirements with respect to sterility of inhalation powders appears to have been factually incorrect. See the carryover paragraph of pages 10-11 of that Response. It is Applicants' current understanding that the FDA may indeed require that such formulations be sterile, though it is unclear when that requirement came into being. At any rate, the point is moot, as Applicants no longer take the position (at least absent further evidence) that there was no motivation in the art to sterilize corticosteroid powders.

As all of the grounds for rejection set forth in the Office action have been overcome, Applicants request that the claims be allowed. The Examiner is invited to telephone the undersigned at 808 986 0300 (after 12:00 noon EST Monday through Friday) if any issues remain. Enclosed is a $702.00 check for excess claim fees and a $980.00 check for the Petition for Extension of Time fee. If there are any other charges or any credits, kindly apply them to Deposit Account 06-1050, referencing attorney docket number 06275-160002.

Respectfully submitted,

Date: December 3, 2004

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